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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,359	11/13/2003	Yie-Hwa Chang	48483-103186	1306

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
07/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/712,359	CHANG ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-18 and 21-38 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 11/10/2008 in response to office action mailed on 07/09/2008 has been acknowledged.

Claims 41 is new

Claims 9-18 and 21-38 and 41 *are pending and are examined in this office action.*

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Applicants' arguments in the response of 11/10/2008 are fully considered while writing this action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-18 and 21-38 are rejected under 35 USC 103 (a) as being unpatentable over Klinkenberg et al (1997, Archives of Biochemistry and Biophysics 347:193-200; art of record) in view of Griffith et al., (1998, Proc. Natl. Acad. Sci. USA 95:15183-15188; art of record) and Fang et al., (Patent No.: US 6,110,744; art of record).

The above claims are drawn to a method of modulating cell proliferation comprising contacting a cell with a polynucleotide variant encoding a dominant negative MetAp2 activity and comprises a translation domain and in further limitation cell is an endothelial cell, polynucleotide is a part of a vector, an adenovirus vector, a CMV promoter, a specific said polynucleotide sequence.

Regarding claims 9-18 and 21-38 Klinkenberg teaches a method of decreasing eukaryotic cell proliferation in vitro using a dominant negative mutant of eukaryotic (yeast)

MetAp1 that lacks the catalytic aminopeptidase activity and interferes dominant negatively with the activity of wild type MetAP1 and MetAp2 and causes slow growth of the cells (entire article; abstract). Klinkenberg further teaches that the observed mutant protein dominant negative activity is due to a competition for binding to a cellular partner and that partner is shared by both MetAP1 and MetAP2 and thus MetAP2 functionally interacts with MetAP1 (P.199, col.1, 2nd paragraph). Klinkenberg further suggests making further mutational studies regarding this interaction with both the MetAPs. Klinkenberg however, does not teach how to make a MetAp2 mutant that lacks activity.

Regarding limitation of making MetAP2 mutant that lacks activity Griffith teaches making and using site-directed mutant of human MetAp2 wherein an amino acid at position 231 is changed (H231N) and found to lose fumagillin binding activity (Abstract, p.15183). Griffith teaches the expression of wild type and said mutant gene (polynucleotide) in endothelial cells (p.15184, col.1, 3rd paragraph). Griffith further teaches that the fact that mutation of His231 (implying any mutation in His231= A231) results in dramatic loss of activity suggests that this residue plays an important role in catalysis by MetAp2 and is this inhibition of MetAp2 enzymatic activity that appears to serve as the molecular basis of inhibition of endothelial cell proliferation in this class of inhibitors (p.15186, col.1, 4th paragraph bridging col.2). Regarding claims 15-16 and 18 of claimed sequences essentially (read as comprising) of identified SEQ ID NO:9 (wild type human) and its variant SEQ ID NO:6 (A231 mutant) and the inherent translation domain are thus taught by Griffith and they are expressed in eukaryotic cells (insect) that inherently contain MetAP2. Griffith however, does not teach a vector containing a polynucleotide encoding a polypeptide is operably linked to a CMV-promoter and does not teach that the vector is adenovirus vector.

Fang teaches an adenovirus vector (see col.13-15) comprising a heterologous gene and a promoter which is a CMV-promoter (col.23, 1st paragraph).

Thus it would have been obvious for one of ordinary skill in the art to substitute the MetAp1 mutant gene producing an catalytically inactive enzyme as taught by Klinkeberg with a MetAp2 mutant gene producing an catalytically inactive enzyme as taught by Griffith and dominant negatively inhibit the cell proliferation in vitro. Further One of skill in

the art could a modify the MetAp2 expression vector of Griffith by using an adenovirus vector containing a CMV promoter as taught by Fang and use it for gene transfer and expression of mutant MetAp2 in endothelial cells. One of ordinary skill in the art would have been motivated to make and use said mutant MetAP2 constructs in order to inhibit the cell proliferation. One of ordinary skill in the art would have reasonable expectation of success making using an inactive MetAp2 mutant because the art teaches that it is routine to make and express inactive MetAp2 mutant gene constructs in a cell in vitro and art further teaches that an inactive MetAp mutant competes with both the wild type MetAps and inhibit cell proliferation. Thus, the claimed invention was *prima facie* obvious.

New claim 41 is rejected for the same reasons as previous claims as above..

Response to Applicants Arguments of 11/10/2008:

The Applicant argues Griffith and or Klingkensberg do not teach or disclose decreasing cell proliferation with the variant MetAP2.as required by claim 9. Hence a combination of Griffith, Klingkensberg and Fang references do not render the invention as claimed obvious.

The Applicants arguments are however found not persuasive because the Applicant first should note should note that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). Further the composition and functions as claimed are presumed inherent. The composition is physically the same it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are

necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) see MPEP § 2112.02. In the instant case the pharmaceutical composition is therapeutically same or an obvious variant of the composition of prior art.

In the instant case the invention as claimed encompasses using the same or similar product namely MetAp2 variant as that of Griffith (e.g., SEQ ID NO:6 claimed in further limitations is essentially same as Grifith's human MetAP2 H231Ala mutant, which Griffith clearly desribes as having no amino peptidase activity. Griffith further clearly teaches having it expressed in a eukaryotic cell which inherently express Met AP2 as taught in the prior art (example see Datta et al, 2000, Biochimie 82:95-107). Although Griffith does not explicitly indicate observing inhibition of cell proliferation in the expressed cells, going by the breadth of instant claims it did as his experiments possess all the elements required.by base claims In the case, such proliferation of inhibition did not occur Griffiths cells expressing said mutant MetAp2, then it is possible unless reasons to believe otherwise, the instant base claims are broad and missing further required or limiting elements that make the invention enabled as claimed. One such possible scenario is that as admitted in the instant invention, the extent of inhibition observed was particularly promoter dependence and/or exhibits dose dependence on the expression levels of the inactive mutant MetAp2 in said cell (see for example Publication. of instant specification: US20050032221 A1; paragraph 50) or it depends on the nature of the expressing cell or cell type. Thus a difference in promoter used or expression levels or the cell type expressed in etc., may explain the difference in observed cell proliferation rates or inhibition of cell proliferation in said cells expressing the same mutant MetAP2 protein.. Hence the rejection is maintained and applied to new claims .as above.

Conclusion:

No claim allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.*, may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/Robert M Kelly/
Primary Examiner, Art Unit 1633